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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,658	01/09/2002	Eric N. Olson	MYOG:024USC1	7444

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,658	OLSON, ERIC N.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 7, 2005 has been entered.

DETAILED ACTION

This application is a continuation of 09/438,075, filed November 10, 1999, now US Patent 6,372,957, which claims benefit to provisional applications 60/107,755, filed November 10, 1998 and 60/108,083, filed November 12, 1998.

Claims 1, 4 and 9 are pending.

Election/Restrictions

Applicant's election without traverse of group III, claims 4 and 9, in the reply filed on April 5, 2004, was acknowledged.

It is noted that claims drawn to non-elected inventions have been cancelled.

However, it is noted that the restriction requirement was set forth as a linked invention and that restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or

otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP ' 804.01.

Response to Amendment

The affidavit from Dr. McKinsey has been filed, and will be discussed as it applies to the rejections below.

Claim Objections

Claim 1 stands objected to because of the following informalities:

As noted previously, Applicants have elected Group III, drawn to a method of treating hypertrophy in a cardiomyoctye comprising the steps of (1) decreasing the expression of MEF2 gene; and (2) further decreasing the expression of a gene that is upregulated by MEF2. Claim 1 is broader than the elected invention. It is noted that claim 1 is a linking claim, however this claim and subject matter has not been found allowable. Accordingly, the scope of the claim should be amended to reflect the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 9 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues that an inappropriately high standard has been made, tantamount to requiring working examples in humans (page 3), and that given the evidence of record and supporting statements in the declaration of Dr. Tim McKinsey the paradigm proposed by the present specification strongly supports MEF2 as a target for treating hypertrophy (pages 4-5 and declaration). See Applicant's amendment, pages 3-5. Applicant's arguments have been fully considered, and have been found persuasive in part.

Initially, it is noted that the Examiner has not required any "experimental evidence" in particular in humans or any other animal model (Applicant's amendment page 3), and notes again that working examples are not even a requirement of an enabling disclosure, though one of the components of the Wands factors in evaluating enablement. In this case the specification provides no working examples that support the claimed invention. Specifically, the claimed invention is a "method of treating hypertrophy" (claim 1), not a potential model system for evaluating the potential affect of a compound on hypertrophy. As stated previously, Examiner

does not contest the evidence of record, in particular that MEF2 is involved in the signaling cascade in cardiac hypertrophy, however as noted previously, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

Applicant's arguments and declaration have been found persuasive in part because given the evidence of record, and the statements of Dr. McKinsey for the interpretation of the cited references, Examiner would agree that the present paradigm for a role of MEF2 in cardiac hypertrophy is supported. While the evidence as a whole has been evaluated in support of the paradigm, it is again noted that in light of the evidence provided by Zhang *et al.* the authors concluded that HDACs "represent *potential* therapeutic targets" (*emphasis added*, Applicant's arguments page 5, citation from page 487, first column), and did not focus on the potential of MEF2 family members even in light of its apparent role. Importantly, it is maintained that providing a characterization of a model system does not necessarily provide enablement for any claimed invention. Again, 35 USC 112, first paragraph, requires that a disclosure enable a claimed invention. In this case, the evidence in the present specification fails to provide the necessary guidance to practice the method as broadly claimed. MEF2 encompasses a family of

related proteins, MEF2A-MEF2D at the time of filing, and while there is evidence that MEF2C plays a role in the signal transduction pathway that is activated during conditions that cause hypertrophy, there is no nexus between this observation and the direct role of all the family members of MEF2 causing hypertrophy. Further, while the evidence of record supports a role for MEF2C in signal transduction during hypertrophy the specification provides insufficient teaching and guidance to the therapeutic methods of treatment as presently claimed.

The claimed invention is directed to a method of treatment where any member of the MEF2 family can be inhibited and any gene up-regulated by any MEF2 family member is inhibited. The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In the context of the claimed invention of treatment, the specification provides no starting materials to practice the claimed invention, no guidance on affecting the treatment, and as noted by Applicant no working examples. While Examiner would agree that

the present specification as supported by the cited art provides a paradigm for studying the role of MEF2C in cardiac hypertrophy, it also demonstrates the complexity of the pathology of hypertrophy. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). As noted previously, in the findings of the Robins court, in a unpredictable area of science an enabling disclosure commensurate in scope of the claimed invention is required (*In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). For example, dependent claim sets forth using an "antisence construct" (claim 9), however there is no sequence for a MEF2 family member set forth, nor what of those sequences is a antisense sequence, or how this is provided in a construct as claimed. Moreover, the breadth of the claims encompass inhibiting any gene up-regulated by a MEF2 family member however there is no specific guidance to what these genes specifically are (noting the specification teaches that fetal genes are affected), and like MEF2 no guidance on the sequences. While what is known in the art does not have to be taught in a specification, the present invention encompasses a method of treatment, and a review of the art of record does not provide support that antisence sequences to MEF2 family members or sequences that inhibit fetal genes were conventional in the art. The claims are very broad in that the instantly claimed method requires further inhibiting genes upregulated by MEF2. In this case, the instant specification does not identify any of these additional potential target genes required to practice the invention. While Examiner would acknowledge that the art teaches that family of MEF2 transcriptional factors regulate the expression of numerous muscle specific and growth factor inducible genes (for example Black *et al.* Ann Rev Cell Dev Bol 14:167-196), neither the art of record nor the instant specification teach which of these should even begin to target to affect hypertrophy. The instantly claimed

method is based in part on the up-regulation of the MEF2 during hypertrophy and the important role of MEF2C in heart growth and development, however, the instant disclosure fails to provide a clear correlation that decreasing any MEF2 family member will affect hypertrophy and fails to provide any specific guidance to what further genes to target for inhibition. Applicant has argued that while "[I]t may be true that inhibiting MEF2 to treat hypertrophy was not well known at the time the present application was filed" but that recent results validate the paradigm on which the instant invention is based (previous amendment page 4). As noted above, Examiner agrees that the paradigm for a role for MEF2C is supported by the instant specification, however this insufficient to enable the method of treatment as presently claimed.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic benefit by *in vivo* or *ex vivo* therapeutic methods; however, the specification does not provide such guidance and fails to provide any correlation between unspecificed compounds, vectors/constructs for antisence sequences, cells comprising vectors, routes of delivery, reimplantation into cells, dosage amounts/frequencies, and fails to provide even any potential starting materials from which the artisan could commence attempting experiments. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court

continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of treatment constitute such a "germ of an idea".

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, for the reasons above and of record, the rejection is maintained.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kobarg *et al.* FEBS Lett. 2005 May 9;579(12):2615-22, "MEF2C DNA-binding activity is inhibited through its interaction with the regulatory protein Ki-1/57", provides further evidence of a role for MEF2C in hypertrophy, however underscores the complexity of the signaling pathway, the potential role in the etiology, and demonstrates that factors that are possible targets encompassed by the claims have yet to be discovered or described even to date.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach